Armed Forces College of Medicine

AFCM

Heart failure (2)

By

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1.Identify positive inotropic drugs used in treatment of heart failure

2.Explain the mechanism of action of positive inotropic drugs

3.Describe the adverse effects and drug interaction of positive inotropic drugs used in treatment of heart failure

HEART FAILURE

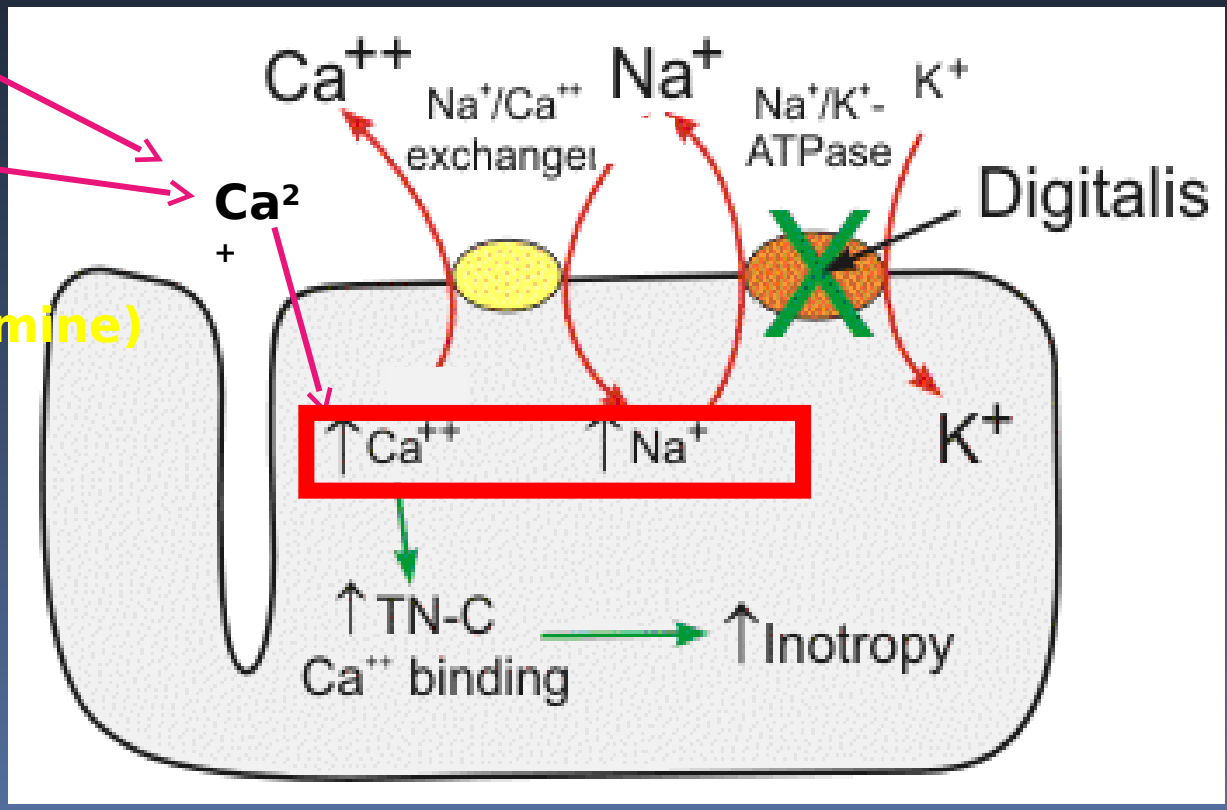
Positive Inotropic Drugs
1. Cardiac Glycosides
Digitalis (Digoxin)

Ca^{2+} channels.

Voltage-gated

Ligand-gated

b_1 Agonist (Dobutamine-Dopamine)



Positive inotropic effect

a. ↓ Venous Pressure:
Due to ↑ COP with better cardiac emptying & subsequent filling; ↓ overstretching of the heart.

b. ↓ Baroreflex sympathetic over-activity:
↓ Peripheral resistance & cardiac loads.
↓ Cardiac over-stimulation (↓ HR).
↓ Renin (↓ Na^+ retention & edema).

c. Diuresis:
Due to ↑ COP →↑renal blood flow & GFR (plus a direct anti-aldosterone action → inhibition of Na^+/K^+ exchange in distal tubules).

Vagal stimulation

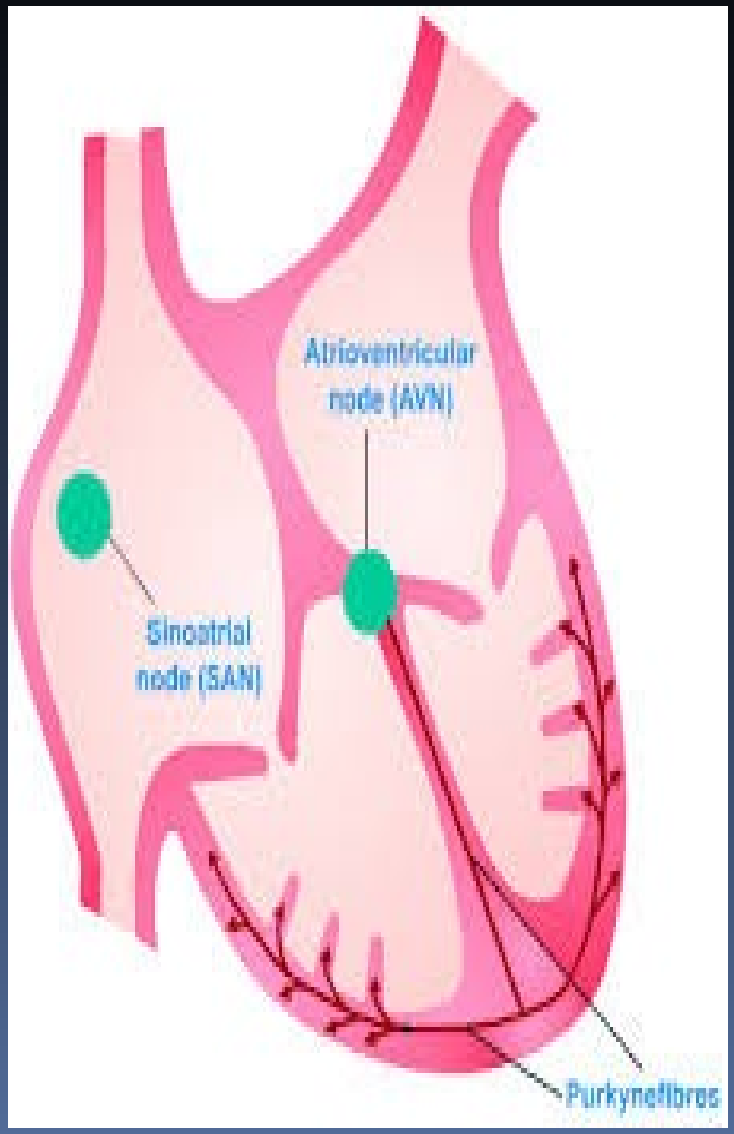
(at therapeutic dose)

-Inhibits SAN →↓ HR

-AVN block →

-Bradycardia, heart block

-Protects ventricle from rapid atrial rate in **atrial flutter and AF.**



Effect on ventricle (toxic dose)

↑Intracellular Na^{+} & Ca^{++} → increase automaticity → ventricular premature beats.

So digoxin:

1-Cause Bradycardia

2-Anti-arrhythmic:In Atrial flutter and atrial fibrillation (protect ventricles)

3- Arrhythmogenic on ventricles: ventricular premature beats, tachycardia, fibrillation

4- Activates K^+ channels → rapidly ends AP → ↓ atrial APD & ERP → converts atrial flutter to atrial fibrillation (AF) &

CNS stimulation

Vagal center stimulation (therapeutic doses).
Vomiting; CTZ stimulation (supratherapeutic doses)
Visual & cortical stimulation→visual disturbances, hallucinations (toxic dose).

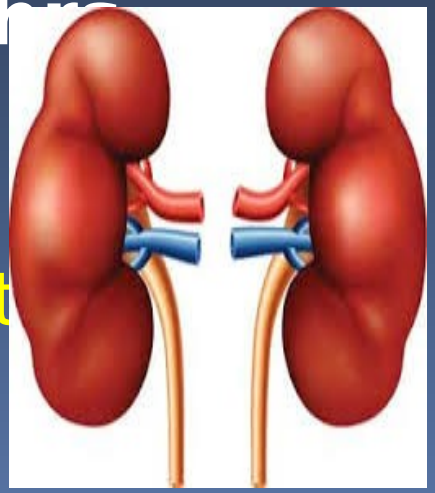
Pharmacokinetics

A: ⅔ of oral dose is rapidly absorbed; rest is inactivated by intestinal flora.

D: ⅔ of drug is unbound to plasma proteins (wide tissue distribution → CNS).

M, E: ⅔ is excreted unchanged renally & rest by stool & hepatically → **$t_{½}$ 36 h**

Narrow safety margin:
therapeutic level (0.5-1.5) close to t
(>2 ng/ml).



Drug Interactions with Digoxin

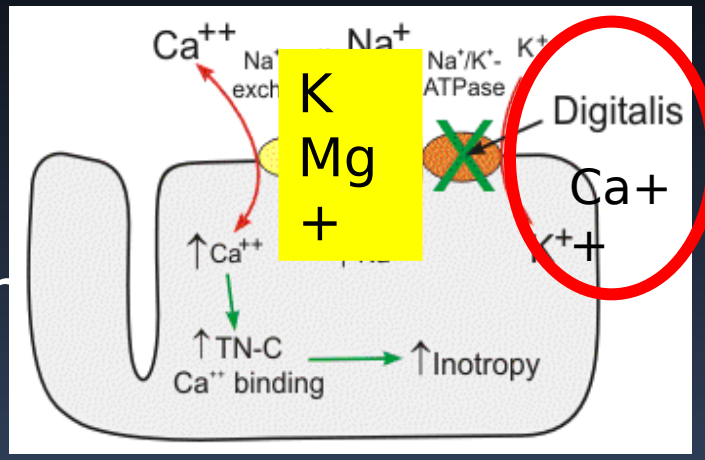
I.Pharmacokinetic Interactions

1. **Erythromycin** →↓ inactivation of digitalis by killing GIT flora→↑absorption.

2- **Metoclopramide** → ↑ GIT motility →↓absorption. . **Anticholinergics** →↓ GIT motility →↑absorption.

3.**Anti-arrhythmics (quinidine, amiodarone & verapamil)**→↓ renal excretion of digoxin & displace it from tissue binding sites & from plasma

II.Pharmacodynamic Interactions



1.Diuretics
(hypokalemia& hypomagnesem
2. Hypercalcemia.
3. Sympathomimetics.

Will increase digitalis induced tachy-arrhythmias

4. b Blockers & CCBs: inhibit SAN & AV node → **complete heart block.**

Indications for Digitalis.

1- chronic HF

A-plus AF (most solid indication): positive inotropic →↑ COP in HF & blocks AVN→ controls ventricular rate in AF.

B-HF despite treatment with diuretics and ACEI

2. Chronic AF without HF:

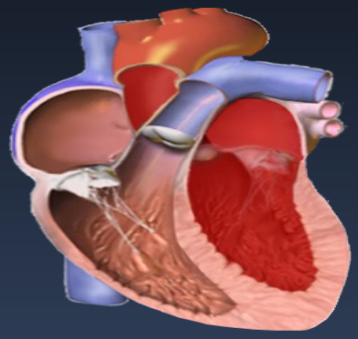
a. Plus verapamil or BB to control ventricular rate.

b. Before procainamide & quinidine to counteract their atropine-like action.

3. Paroxysmal supraventricular tachycardia: vagal effect on AVN ends attack.

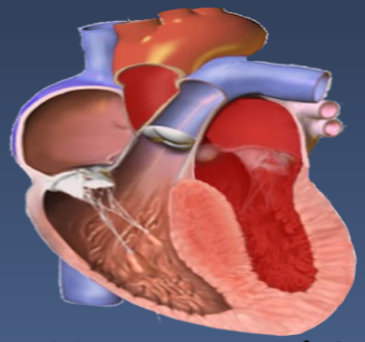
Contraindications

1. Acute MI & rheumatic carditis (irritable myocardium → arrhythmia).
2. HOCM: inotropic →↑ outflow tract obstruction



Normal

3. AF+WPW: paradoxical↑ HR (blocks AVN →↑ conduction in accessory tract).
4. Partial/ incomplete heart block → converted to complete heart block (vagal effect).
5. Ventricular tachycardia →



Hypertrophic

Digitalis Toxicity (GCCG)

1. **G**IT Upsets: anorexia, nausea, vomiting and diarrhea (early symptoms).
2. **C**ardiac Arrhythmia:

a. Supraventricular & ventricular; premature beats, tachycardia or fibrillation.

b. Sinus bradycardia and heart block (↑ vagal tone).

3. **C**NS manifestations: confusion, hallucination, yellow & green colored vision.
4. **G**ynecomastia (steroid nucleus).

Treatment of Toxicity

1.Stop digitalis & the K losing diuretic.

2. KCl: if serum potassium is < 3.5 mmol/l; C.I. in heart block.

3. Lidocaine or phenytoin in V. arrhythmia.

4. Atropine in bradycardia and heart block.

5. Digibind (fab): antibodies that bind digoxin → eliminated in urine (in fatal toxicity).

Phosphodiesterase III Inhibitors

Milrinone – Inamrinone

Mechanism:

Inodilators, inhibit phosphodiesterase III→↓ cAMP breakdown:

1. ↑ cardiac contractility → ↑COP.
2. Vasodilation → arterial (↓ afterload & PR), venous dilators (↓preload & pulmonary congestion) →↓ left & right cardiac filling pressures.

Indications:

Short term treatment of HF especially, acute or chronic refractory.

Adverse Effects:

GIT upset.

Thrombocytopenia - arrhythmia.

↓ Preload

Improve congestion

- Salt & Fluid restriction, Diuretics,Venodilators
- CHF: Loop diuretic, ACEIs, ARBs, Nitrates
- AHF:Loop diuretics, Nitrates.Nitroprusside

↓ Afterload

Improve low COP

- Arteriodilators
- CHF:ACEIs, ARBs., Hydralazine
- AHF:Nitroprusside

↑Contractility

Improve low COP & congestion

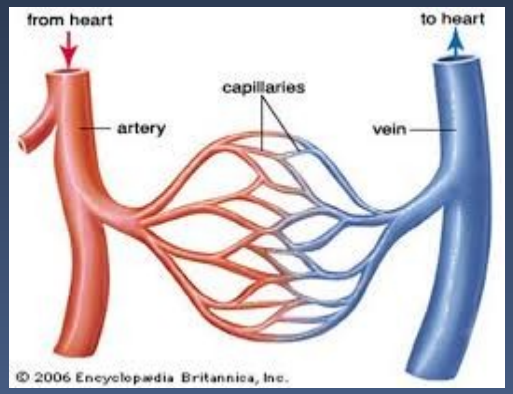
- Positive inotropics
- CHF:Digoxin
- AHF:Dopamine.Dobutamine.Inamrinone

Protect Heart &/or restore its function

- CHF:β-blockers:Carvedilol , Bisoprolol, Metoprolol
- Aldosterone antagonists: Spironolactone, Eplerenone

The new ARNI (angiotensin receptor neprilysin inhibitor) sacubitril-valsartan is used in place of ACEI (or ARB) in patients with class II - IV HF + LVEF ≤40 % with persistent symptoms despite optimal combination therapy. Some clinicians use it from the start.

-ACEIs, ARBs are mixed arteriovenodilators.



- Mortality rate in HF (30% per year) is ↓ by ACEIs, ARBs, βBs & spironolactone.

Lecture quiz

Which of the following is important to monitor in patients taking digoxin?

A.Chloride

B. Potassium

C. Sodium

D. Zinc

E. calcium

Lecture quiz

- Which of the following describes the mechanism of action of milrinone in HF?

A. Decreases intracellular calcium

B. Increases cardiac contractility

C. Decreases cAMP

D. Activates phosphodiesterase

E. Antiarrhythmic

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

Thank You